AMD070

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

The investigational agent AMD070, also known as AMD11070, is a specific and reversible CXCR4 inhibitor. AMD070 is a derivative of AMD3100, a previously studied investigational CXCR4 inhibitor. [1] [2] [3]

HIV/AIDS-Related Uses

AMD070 is an investigational agent with in vitro activity against HIV-1. The safety, tolerability, dosing, and pharmacokinetics of AMD070 are being studied in Phase I and II clinical trials. A Phase II trial to evaluate safety and efficacy has been suspended.[4] [5] [6]

Pharmacology

AMD070 prevents viral entry into cells by binding to the chemokine receptor CXCR4, the coreceptor used by CXCR4-tropic HIV for membrane fusion and viral entry. AMD070 does not bind to CCR5, the coreceptor that mediates entry of macrophage-tropic HIV. The CXCR4 strains are considerably more pathogenic; their appearance late in HIV infection correlates with CD4 count decline and rapid disease progression.[7]

AMD070 has not yet been fully evaluated in human trials. A small Phase I safety study of AMD070 in HIV uninfected male volunteers evaluated the safety, pharmacokinetic profile, and bioavailability of single and multiple doses of AMD070. Thirty subjects participated in this study. Single doses of 50, 100, 200, and 400 mg and multiple doses of 100, 200, and 400 mg twice daily (five doses, with pharmacokinetic sampling performed following the last dose) were examined. Dose-dependent increases in the peak plasma concentration (Cmax) and the median area under the concentration-time curve (AUC) were observed following both single and multiple doses. Evidence of AMD070 accumulation was noted with repeated administration.[8]

AMD 070 is readily absorbed in humans after oral administration.[9] When studied in HIV infected patients with CXCR4-tropic virus, AMD070 displayed a greater-than-proportional increase in exposure across 100 and 200 mg twice-daily dosage groups, consisting of eight and two participants, respectively. Mean Cmax were 346.5 ng/ml and 1,271.2 ng/ml in the 100 and 200 mg groups, respectively. Mean AUC were 1,123.5 mg(h)/ml and 6,471.8 ng(h)/ml in the same groups, respectively. The half-life of 200 mg AMD070 twice daily was 5.5 h. AMD070 accumulates with repeat administration, although minimum plasma concentrations in this study did not achieve steady-state levels after 10 days of administration.[10] AMD070 Cmax, AUC, and half-life are increased when administered concurrent with steady-state levels of ritonavir as a pharmacokinetic booster.[11]

Because no information concerning the reproductive toxicity of AMD070 is currently available, AMD070 is not being tested in women at this time, and male volunteers in AMD070 clinical trials are advised to avoid participating in conception activities during AMD070 administration and for 2 weeks after stopping the drug.[12] AMD070 is not mutagenic in vitro; however, CXCR4 may play a role in hematopoiesis in utero.[13]

AMD070 is 84% to 97% protein bound at pharmacologically active concentrations; however, protein binding does not appear to have a significant effect in vitro. Limited information is available concerning the metabolism of AMD070. AMD070 represents the major circulating form of the drug in plasma; several putative metabolites have been noted in plasma samples from in vivo preclinical studies.[14] Based on preliminary laboratory studies, AMD070 is a substrate for cytochrome P450 (CYP) 3A4 but has a low potential for induction. AMD070 moderately inhibits CYP2D6 and exhibits time-dependent inhibition of CYP3A4.[15]

Median total body clearance of AMD070 is 216 l/hr. AMD070 is eliminated in at least a biexponential manner, and the median terminal half-life is 16 hours.[16] [17]

AMD070 appears to share nearly overlapping

Pharmacology (cont.)

binding sites with a previously investigated CXCR4 inhibitor, AMD3100. However, the amino acid residue D97 on the CXCR4 receptor interacts specifically with AMD070 alone. Decreased AMD070 binding potency of more than 100-fold has been associated with W94A, D97N, D171N, and E288A mutations. Binding potency decreases of 10- to 50-fold have been observed with 445A and D262N mutations.[18]

A small safety trial of AMD070 monotherapy for 10 days compared 100 and 200 mg twice-daily dosages in eight and two participants, respectively. All patients had CXCR4- or mixed-tropic virus and were treatment-naive or at least free from antiretroviral treatment for 14 days. By Day 5, two of four responding participants experienced a tropism switch to CCR5-tropic virus, and one more participant experienced a tropism switch at Day 10.[19]

Adverse Events/Toxicity

Because AMD070 and AMD3100 are both investigational CXCR4 inhibitors and AMD070 is a derivative of AMD3100,[20] the adverse events reported for AMD3100 may be similar to those for AMD070. In a study of 40 HIV infected people, AMD3100 was administered intravenously via a 10-day continuous infusion up to 160 mcg/kg/hour. The most common subjective complaints from study participants, regardless of whether they were attributed to study drug, included diarrhea (48%), flatulence (43%), headache (40%), nausea (35%), abdominal pain (33%), abdominal distension (25%), tachycardia (25%), dizziness (25%) and paresthesias (23%). Vital sign abnormalities, including hypertension (67%), hypotension (25%), and tachycardia (47%), were observed transiently in many participants, although there were no dose-related trends. Several-fold increases in white blood cells, CD4 counts, and lymphocytes were seen in all participants but were not of clinical concern.[21]

In a small, Phase I safety study of AMD070 in HIV uninfected volunteers, the drug was generally well tolerated; 3 of 12 participants complained of a transient, mild-to-moderate headache after taking a single dose of AMD070 on an empty stomach.[22] No serious adverse events were reported, and adverse events were generally mild (mainly Grade 1 or 2). The most common adverse effects were pain, gastrointestinal disturbances, and Grade 1 tachycardia; other reported events included lightheadedness, palpitations, insomnia, shaky and unsteady hands, a flushed feeling, seasonal allergies, a buzzing sensation, and heartburn.[23]

Short-term administration has a potential for acute gastrointestinal toxicity, characterized by vomiting and diarrhea that usually occurs within 1 to 2 hours of administration. These effects are expected to be transient. Bone marrow hypocellularity has been observed at the highest dose levels; reversibility of this effect has not been demonstrated. Lymphoid atrophy has been observed in the thymus, lymph nodes, and spleen. Heart rate elevations and blood pressure changes have also been noted.[24]

Dosages of 200 mg AMD070 twice daily for 10 days have been well tolerated in HIV infected patients. No Grade 3 or greater toxicities were observed during and up to 7 days after treatment.[25] In two small studies of 100 or 200 mg AMD070 twice daily, given alone or coadministered with ritonavir, no serious, drug-related adverse events or laboratory abnormalities were reported. The most common adverse effects experienced in HIV infected patients taking 10-day monotherapy were mild gastrointestinal symptoms and headache.[26] [27]

Drug and Food Interactions

In animal studies, the bioavailability of AMD070 was substantially reduced when the drug was administered 30 minutes after a meal. Current studies are investigating AMD070 when administered both on an empty stomach and with food.[28] In a small study of HIV uninfected volunteers, absorption of AMD070 did not appear affected by food.[29]

In vitro studies using five different CD4 cell lines, CXCR-transfected cell lines, and peripheral blood mononuclear cells indicated that AMD070 had additive or synergistic antiviral activity when combined with other known HIV inhibitors, including fusion inhibitors (enfuvirtide), nucleoside

Drug and Food Interactions (cont.)

reverse transcriptase inhibitors (zidovudine and tenofovir), and protease inhibitors (amprenavir).[30]

Because AMD070 is a substrate of CYP3A4 and p-glycoprotein, it will likely be administered with a ritonavir booster. The hypothesis of favorably altered pharmacokinetics of AMD070 was tested in healthy volunteers, who received single doses of 200 mg AMD070 on Days 1, 3, and 17, and ritonavir 100 mg every 12 hours on Days 3 through 18. Ritonavir boosting at steady-state decreased the time to maximum concentration of AMD070 by 25%, increased the Cmax of AMD070 by 47%, increased the AUC of AMD979 by 24%, and increased the half-life of AMD070 by 16%.[31]

As a substrate of CYP3A4, AMD070 has low induction potential and time-dependent inhibition activity. In addition, AMD070 is a moderate inhibitor of CYP2D6. When a single dose of AMD070 was tested in combination with midazolam, a CYP3A4 substrate, and dextromethorphan, a CYP2D6 substrate, statistically significant increases in AUC were observed for both midazolam and dextromethorphan. A statistically significant increase in Cmax of dextromethorphan was observed as well. The clinical effects and dose-altering requirements of these increases are unknown.[32]

Clinical Trials

For information on clinical trials that involve AMD070, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: AMD070 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[33]

Dosage Form: AMD070 has been studied in doses of 50, 100, 200, and 400 mg.[34] Dosages of 100 mg and 200 mg AMD070 twice daily have been studied for up to 10 days in Phase II trials.[35]

Storage: Store between 2 C and 8 C (36 F to 46 F) and protect from moisture.[36]

Chemistry

CAS Name: AMD 070[37]

CAS Number: 690656-53-2[38]

Physical Description: Solid crystalline.[39]

Stability: After the bottle is opened, AMD070 capsules have a shelf-life of 28 days.[40]

Other Names

AMD11070[41]

070[42]

AMD 070[43]

Further Reading

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Manufacturer Information

AMD070
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Cambridge, MA 02142
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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